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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/982,223	10/18/2001	George Q. Daley	13086-002001	7405

26161 7590 09/23/2003

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EXAMINER
LAMBERTSON, DAVID A

ART UNIT	PAPER NUMBER
1636	15

DATE MAILED: 09/23/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/982,223	DALEY ET AL.	
	Examiner	Art Unit	
	David A. Lambertson	1636	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *08 July 2003* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-33* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-33* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) *8,11* .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other:

DETAILED ACTION

Election/Restrictions

Applicant's election with traverse of Group II in Paper No. 13 is acknowledged. The traversal is found persuasive and the claims of Groups I and II are rejoined.

Claims 1-33 are pending and ready for examination in the instant application, and an Office Action on the merits is contained herewith.

Priority

Applicant's claim for domestic priority to US Application 60/241,879 under 35 U.S.C. 119(e) is acknowledged.

Information Disclosure Statement

The information disclosure statement filed February 28, 2002 and December 9, 2002 as Paper Nos. 8 and 11 have been considered, and a signed and initialed copy of the form PTO-1449s are attached to this Office Action.

It is noted that one of the references has been lined through as not being considered. This reference (ALL) was not provided with the IDS; instead a different reference was provided (Carnero *et al.*, *Nucleic Acids Research* **28**(11): 2234). Since it is unclear which reference was supposed to be considered, neither reference has been considered.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 25 and 32 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Applicant claims a vector comprising a bacterial origin of replication wherein a portion of the origin of replication has been removed. The claims read on a broad genus of bacterial origin of replication fragments that can be used upon the removal of an undisclosed portion of the bacterial replication origin.

The written description requirement for a claimed genus may be satisfied through sufficient description of a representative number of species by actual reduction to practice or by disclosure of relevant identifying characteristics, i.e. structure or other physical and/or chemical properties, by functional characteristics coupled with a known or disclosed correlation between function and structure, or by a combination of such identifying characteristics sufficient to show applicants were in possession of the claimed genus. In the instant case, the specification does not sufficiently describe a representative number of species by actual reduction to practice or by disclosure of relevant identifying characteristics.

Applicant claims the use of a bacterial origin of replication fragment by function only, without any disclosed or known correlation between the elements and their function. The specification does not teach what portions of the bacterial origin of replication can be removed and result in the retention of its function. Furthermore, the instant specification does not teach

what portion of any bacterial origin of replication is absolutely necessary for it to function in the vector as claimed. In essence, the instant claims lay claim to a functional portion of a bacterial origin of replication without describing what portion of a bacterial origin of replication must be retained/can be deleted and retain functionality. The skilled artisan cannot envision a sufficient number of embodiments of the instant invention from the instant specification, therefore the specification has not satisfied the written description requirement.

The prior art does not provide sufficient information on the subject to overcome the deficiencies of the instant specification. There is no description in the prior art that allows one to envision a representative number of functional fragments of bacterial origins of replication by disclosing their structural or functional features so that one of skill in the art could envision the claimed invention. Thus the skilled artisan cannot rely on the prior art to envision a sufficient number of embodiments of the instant invention to see that the applicant was in possession of the claimed genus.

Neither the specification of the instant application nor the prior art teaches a structure-function relationship for a representative number of functional fragments of a bacterial origin of replication. As a result, the skilled artisan would not be able to envision the claimed invention by relying on the teachings of the prior art or the instant specification. Therefore applicant has not satisfied the written description requirement to show the skilled artisan that they were in possession of the claimed genus.

Claims 29-33 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one

skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Applicant claims a viral vector that can express a heterologous insert sequence that is greater than 8 kilobases (kb) in length. The claims read on a broad genus of viral vectors having the ability to functionally express a heterologous sequence of a greater than 8kb in length.

The written description requirement for a claimed genus may be satisfied through sufficient description of a representative number of species by actual reduction to practice or by disclosure of relevant identifying characteristics, i.e. structure or other physical and/or chemical properties, by functional characteristics coupled with a known or disclosed correlation between function and structure, or by a combination of such identifying characteristics sufficient to show applicants were in possession of the claimed genus. In the instant case, the specification does not sufficiently describe a representative number of species by actual reduction to practice or by disclosure of relevant identifying characteristics.

Applicant claims a viral vector that can express a heterologous insert sequence that is greater than 8 kb in length by function only, without any disclosed or known correlation between the elements and their function. The specification does not teach what structural features of a vector permit the expression of insert sizes that are greater than 8kb in length. There is no correlation between the particular vectors, or a feature therein, and the ability to express a sequence of greater than 8kb in length recited in the specification. Thus, the skilled artisan would have no way of discerning which viral vectors would have this functional property by observing the features of the vector. As a result, the skilled artisan cannot envision a sufficient number of viral vectors that can express a heterologous insert sequence that is greater than 8 kb

in length from the instant specification. Therefore, the instant specification does not meet the written description requirement for the indicated claims.

The prior art does not provide sufficient information on the subject to overcome the deficiencies of the instant specification. There is no description in the prior art that allows one to envision a representative number of viral vectors that can express a heterologous insert sequence that is greater than 8 kb in length by disclosing structural or functional features of a vector so that one of skill in the art could envision that a viral vector has the ability to express such a sequence. Thus the skilled artisan cannot rely on the prior art to envision a sufficient number of embodiments of the instant invention to see that the applicant was in possession of the claimed genus.

Neither the specification of the instant application or the prior art teaches a structure-function relationship for a representative number of viral vectors that can express a heterologous insert sequence that is greater than 8 kb in length. As a result, the skilled artisan would not be able to envision the claimed invention by relying on the teachings of the prior art or the instant specification. Therefore applicant has not satisfied the written description requirement to show the skilled artisan that they were in possession of the claimed genus.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1-33 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 1 recites the limitation "or a portion thereof" in reference to a packaging sequence that is present in the claimed vector. There is insufficient antecedent basis for this limitation in the claim. In part (a) of the claim, the limitation "a packaging sequence" is recited. The claim is indefinite because it is unclear if the vector must contain a packaging sequence, or if it can merely contain a portion of a packaging sequence as set forth in the body of the claim. The claims depending on claim 1 do not remedy this indefiniteness.

Claims 13, 28 and 29 recite the term "proviral recovery sequence" in the claim, but it is unclear what the limitation is intended to mean. A search of the popular literature does not indicate that this term is well known in the art. Consultation with the specification indicates on page 49, lines 4-20, that a "proviral recovery sequence allows for excision of retroviral provirus from the genome of a host cell..." and "...can include at least one recombinase site and/or at least one, two, three, four, five or more, rare cutter restriction site(s)." However, this definition is indefinite because of the recitation of the word "can" in the definition. It is unclear from this definition what else *can* be considered a proviral recovery sequence, or if the recombinase and rare cutter sites are the only representatives of a proviral recovery sequence. As a result, the recitation of the limitation "proviral recovery sequence" renders the claim indefinite. The claims depending on claims 13, 28 and 29 do not remedy this indefiniteness.

Claims 24-27 recite the limitation "viral vector" in reference to claim 13. There is insufficient antecedent basis for this limitation in the claim. Claim 13 does not recite the

limitation "viral vector" in any portion of the claim. Therefore, it is unclear what limitation is being referred to in this claim.

Claim 26 recites the limitation "the bacterial marker sequence" in reference to claim 13. There is insufficient antecedent basis for this limitation in the claim. Claim 13 does not recite the limitation "bacterial marker sequence" in any portion of the claim. Therefore, it is unclear what limitation is being referred to in this claim.

Claims 26, 28 and 29 recite the limitation "bacterial marker" without defining the term "bacterial marker." It is unclear if a bacterial marker represents a selectable marker, such as the ampicilin resistance marker, kanamycin resistance marker, etc., or if bacterial marker sequence is meant to also include sequences that are specific to bacteria that can be used as an identification marker (e.g., by Southern Blot). Because the term is not properly defined in the claims or the specification, the claim is rendered indefinite.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.
>
> (e) the invention was described in a patent granted on an application for patent by another filed in the United States before the invention thereof by the applicant for patent, or on an international application by another who has fulfilled the requirements of paragraphs (1), (2), and (4) of section 371(c) of this title before the invention thereof by the applicant for patent.

Prior to setting forth the rejections under 35 USC 102, the Examiner wishes to clarify the interpretation of some terms in the claims. First, there is no clear definition of the term "altered" set forth in the specification. Therefore, the term is interpreted as broadly as possible, and encompasses any and all alterations, including deletions as well as substitutions. Second, the term "proviral recovery sequence" is indefinite in its meaning as set forth above under 35 USC 112, second paragraph. In the interest of compact prosecution, the term is being interpreted as broadly as possible, and includes any sequence that would allow the excision and recovery of the viral insert. This includes an LTR region, which is the functional part of a virus that allows its excision from the genome under normal conditions. Finally, with respect to the "packaging sequence" limitation of the claim, the claim is being interpreted to include any portion of the "packaging sequence" (as set forth in the body of the claim), which is the broadest interpretation of the claim.

Claims 13, 16, 17, 23, 27 and 28 are rejected under 35 U.S.C. 102(b) as being anticipated by Bender *et al.* (IDS reference AL; see entire document; henceforth Bender).

Bender teaches a retroviral vector comprising a 5' LTR, the packaging sequence (a.k.a., psi or ψ) from Moloney Murine Leukemia Virus (henceforth MoMuLV), a heterologous insert sequence consisting of a bacterial selection marker less than 600 bp in length (e.g., hygromycin/*hph* gene), and a 3' LTR (see for example Figure 1 and page 1640, left column, first complete paragraph). Bender also teaches adding an amino terminal portion of the MoMuLV *gag* sequence, mutated at its initiation ATG codon, to the packaging sequence, and that this addition increases the titer (a measure of the infectivity/effectiveness of the viral vector) of the

vector (see for example page 1642, right column, bridging paragraph). Therefore, Bender anticipates a viral vector comprising a packaging sequence (psi/*gag* amino terminus fusion) with at least one ATG codon altered, a heterologous insert sequence (*hph*) that is a bacterial marker sequence of less than 600 base pairs in length, and a proviral recovery sequence (LTR).

The changes made to 35 U.S.C. 102(e) by the American Inventors Protection Act of 1999 (AIPA) and the Intellectual Property and High Technology Technical Amendments Act of 2002 do not apply when the reference is a U.S. patent resulting directly or indirectly from an international application filed before November 29, 2000. Therefore, the prior art date of the reference is determined under 35 U.S.C. 102(e) prior to the amendment by the AIPA (pre-AIPA 35 U.S.C. 102(e)).

Claims 1-5, 7, 11, 12-18, 22-23 and 27 are rejected under 35 U.S.C. 102(e) as being anticipated by Kingsman *et al.* (US Patent No. 6,235,522; see entire document; henceforth Kingsman).

Kingsman teaches a retroviral vector comprising a 5' LTR, a portion of the HIV1 *gag* packaging sequence gene (specifically nucleotides 791-1143 of the full length sequence, which corresponds to the amino-terminal region of HIV *gag*) altered at its three ATG codons (including the *gag* initiator codon, a multicloning site (comprising a number of restriction sites for the insertion of a heterologous gene), and a 3' LTR (i.e., a proviral recovery sequence) (see for example Figure 3, in combination with column 7, lines 53-58, and column 9, line 43). Kingsman meets the limitation of claim 5 because the amino terminal portion of the *gag* sequence of the vector described in Kingsman is used, thus as indicated in the instant claims, the amino terminal portion of the *gag* sequence is altered in at least two codons. Additionally, Kingsman meets the

limitation of claim 11 because all three of the nucleotides of the initiation codon are altered (ATG->TAA; see SEQ ID NO: 1, residues 21-23, at column 8, lines 15-16). Finally, Kingsman teaches that a heterologous insert sequence can be cloned into the vector (see for example column 4, lines 18-40) for gene therapy or marker expression purposes.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Prior to setting forth the rejections under 35 USC 103, the Examiner wishes to clarify the interpretation of some terms in the claims. First, there is no clear definition of the term "altered" set forth in the specification. Therefore, the term is interpreted as broadly as possible, and encompasses any and all alterations, including deletions as well as substitutions. Second, the term "proviral recovery sequence" is indefinite in its meaning as set forth above under 35 USC 112, second paragraph. In the interest of compact prosecution, the term is being interpreted as broadly as possible and includes any sequence that would allow the excision and recovery of the viral insert. This includes an LTR region, which is the functional part of a virus that allows its excision from the genome under normal conditions. Finally, with respect to the "packaging sequence" limitation of the claim, the claim is being interpreted to include any portion of the packaging sequence (as set forth in the body of the claim), which is the broadest interpretation of the claim.

Claims 24, 28, 29 and 31 are rejected under 35 U.S.C. 103(a) as being unpatentable over Beach *et al.* (US Patent No. 6,255,071; see entire document; henceforth Beach) in view of Bender as applied to claim 13 (as well as claims 16, 17, 23, 27 and 28) under 35 USC 102(b).

Beach teaches a retroviral vector comprising, a 5' LTR, a packaging sequence from MoMuLV (e.g., psi), a polylinker site (i.e., restriction sites for the cloning of heterologous sequences), a bacterial origin of replication, and any bacterial selection marker (see for example Figure 1, column 5, lines 9-22 and column 6, lines 61-65). Significantly, Beach also teaches what is referred to as a "proviral excision element" (see for example Figure 1 and column 5, lines 9-22), which includes the use of recombinase sites and rare-cutting restriction enzymes (see for example column 6, lines 8-19). Absent any evidence to the contrary or any indication of what structural/functional features of a vector prevent or allow the expression of an 8kb heterologous insert sequence (see the rejection of claims 29-33 under 35 USC 112, first paragraph as set forth above), the vector that Beach teaches is considered to be capable of expressing a heterologous insert of greater than 8kb in length. However, Beach does not teach the alteration of at least one ATG codon in the packaging sequence.

Bender teaches the same elements as set forth in the rejections under 35 USC 102(b). Briefly, Bender teaches that the addition of an amino terminal portion of the MoMuLV *gag* sequence, with its initiator ATG codon altered, to the MoMuLV packaging sequence (i.e., psi) increases the titer of a viral vector.

It would be obvious to the ordinary skilled artisan to combine the teachings of Beach and Bender because both teachings regard the production of an effective retroviral vector that

includes the same functional elements (e.g., LTRs, the MoMuLV packaging sequence, etc.), therefore the teachings can be combined effectively. The ordinary skilled artisan would be motivated to add the feature of an amino terminal MoMuLV *gag* sequence with its initiator ATG codon altered (taught by Bender) to the vectors taught by Beach because the addition of this sequence increases the titer of the viral vector (as Bender teaches), and it is desirable to obtain a vector having the highest effective level of infectivity.

Absent evidence to the contrary and given the teachings of the stated prior art and the high level of skill of the ordinary skilled artisan at the time of the applicant's invention, it must be considered that said ordinary skilled artisan would have had a reasonable expectation of success in practicing the claimed invention.

Claims 26 and 33 are rejected under 35 U.S.C. 103(a) as being unpatentable over Beach in view of Bender as applied above to claims 24 and 29 (as well as claims 28 and 31), and in further view of Luo *et al.* (US Patent No. 6,114,111; see entire document; henceforth Luo).

Beach in view of Bender teaches all of the elements as set forth above in the rejection of claims 24 and 29 (as well as claims 28 and 31) under 35 USC 103(a). However, although Beach suggests that any bacterial selectable marker can be used (see for example column 6, lines 61-65), neither Beach nor Bender explicitly suggests the use of bleomycin as a selectable marker.

Luo teaches that selection genes such as bleomycin are well known in the art, and should be applied to mammalian cells for the purpose of selecting cells that contain a vector of interest (see for example column 7, lines 1-18). Luo also states that the particular selection marker used varies with the cell being transfected/transformed (see column 7, lines 5-6).

It would be obvious to combine the teachings of Beach in view of Bender with those of Luo because both teachings describe vector systems that make use of bacterial selection markers, and Beach goes so far as to suggest that any bacterial selection marker can be used, of which bleomycin was a well known marker as taught by Luo. The ordinary skilled artisan would be motivated to combine these teachings because Beach indicates that any bacterial selection marker can be used in the selection of transfected cells, Luo indicates that bleomycin is a well known and suitable selection marker for selection of transfection events, and it would be desirable to use a plethora of different selection markers in order to ensure that all types of cells can be selected for, as suggested by Luo when they indicate that the selection marker needs to be varied with respect to the cell type being selected.

Absent evidence to the contrary and given the teachings of the stated prior art and the high level of skill of the ordinary skilled artisan at the time of the applicant's invention, it must be considered that said ordinary skilled artisan would have had a reasonable expectation of success in practicing the claimed invention.

Allowable Subject Matter

No claims are allowable.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to David A. Lambertson whose telephone number is (703) 308-8365. The examiner can normally be reached on 6:30am to 4pm, Mon.-Fri., first Friday off.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Remy Yucel, Ph.D. can be reached on (703) 305-1998. The fax phone number for the organization where this application or proceeding is assigned is (703) 872-9306.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 308-0196.

David A. Lambertson
AU 1636

GERRY LEFFERS
PRIMARY EXAMINER